

Clinical Investigation

Symptoms and Routine Laboratory Abnormalities Associated With Coccidioidomycosis

MICHAEL L. YOZWIAK; LINDA L. LUNDERGAN, MD; STEVEN S. KERRICK, MD; and JOHN N. GALGANI, MD, Tucson

To assess the relationships of various symptoms and other early findings to the diagnosis of primary coccidioidomycosis, we devised a 40-question survey that was completed by 556 college students seeking medical care for illness possibly due to Coccidioides immitis. The results of routine laboratory studies on these patients were also compiled. Of 269 who had coccidioidal antibody determinations and other diagnostic tests, coccidioidomycosis was diagnosed in 36 (13%). By logistic regression procedures, an elevated erythrocyte sedimentation rate, male gender, "red lumps on shins," recent arrival to an endemic area, acuteness of symptoms, and decreased total peripheral blood lymphocyte counts were independent factors positively associated with infection ($P < .05$). Relative risk analysis indicated that 60% of patients with four or more of these factors were found to have coccidioidomycosis. Other significantly but not independently associated factors were an increased total leukocyte count, chest pain with breathing, fever, an absence of hoarseness, and an abnormal chest roentgenogram.

(Yozwiak ML, Lundergan LL, Kerrick SS, et al: Symptoms and routine laboratory abnormalities associated with coccidioidomycosis. West J Med 1988 Oct; 149:419-421)

For college students in regions endemic for *Coccidioides immitis*, about 4 per 1,000 each year seek medical attention with symptoms related to coccidioidomycosis.¹ Numerous symptoms and other findings have been associated with infection, including fatigue, cough, abnormal roentgenogram of the chest, chest pain, rash, and male gender.² Little information exists, however, regarding the specificity of these or other associated findings. Thus, it is not known whether any are of value to assist in diagnosing coccidioidomycosis. In an attempt to elucidate this question, we embarked on a prospective study of patients' demographic factors, symptoms, and routine laboratory measurements in relationship to a subsequent diagnosis of coccidioidal infection. The results of this effort are the subject of the present report.

Patients and Methods

A questionnaire was developed by a consensus of physicians who were familiar with coccidioidomycosis. The survey contained 40 questions in the general content areas of demographics and pulmonary and nonpulmonary symptoms (a copy of the complete questionnaire is available on request from the corresponding author). The questionnaire was distributed from September 1984 to March 1986 to any student seen at the University of Arizona (Tucson) Student Health Service who would subsequently be skin tested for coccidioidomycosis. Most of these students were otherwise healthy and had no knowledge or roentgenographic evidence of a previous coccidioidal infection.

Subsequent medical care was provided by one of eight physicians on the staff irrespective of participation in the

survey; further evaluation for the possibility of coccidioidal infection was at the physician's discretion. If coccidioidal infection was considered possible, the evaluation included tests for coccidioidal antibodies,^{3,4} skin testing with coccidioidal antigen,⁵ a roentgenogram of the chest, and a complete blood count. Many patients with negative skin tests were retested within a month to determine if a change in skin test status had occurred. Other tests were repeated as deemed necessary.

As a result of these evaluations, patients were categorized into one of three groups: a diagnosis of recent coccidioidal infection could be established (case), a diagnosis of recent coccidioidal infection could not be established (noncase), or insufficient information was available to determine whether the patient had a coccidioidal infection (indeterminate). To be included as a case required at least one of the following criteria: detectable serum precipitating-type antibodies³ or complement-fixing antibodies for coccidioidin^{3,4} at a minimum of 1:2 serum dilutions, or cutaneous hypersensitivity to coccidioidin 1:100 (Iatric Corporation, Tempe, Ariz) only if a similar skin test were found to be nonreactive within the previous month. For the purposes of this analysis, noncases had at least one serologic study and neither of the two diagnostic criteria were met. The remaining patients were classified as indeterminate.

Data from the questionnaires and laboratory studies were entered into a data base (R:base 5000, Microrim, Inc, Bellevue, Wash) and analyzed using a statistical applications program (Systat, Systat Inc, Evanston, Ill).

The initial review consisted of examining the distributions of responses for each question and laboratory measure-

TABLE 1.—Symptoms and Routine Laboratory Abnormalities Independently Associated With Coccidioidal Infection

Variable	P Value	Relative Risk	Risk
Erythrocyte sedimentation rate . .	<.001	.247	>28 mm/hr
Gender007	.195	Male
"Red lumps on shins"004	.174	Present
Years residence in endemic area . .	.001	.160	<4 yr
Duration of symptoms	<.001	.128	<1 wk
Number of lymphocytes050	.091	<1,570/ μ l

ment in the entire sample. Continuous variables were then arbitrarily divided into ranges for further analysis. Relatedness of these groups to the diagnosis of coccidioidal infection was determined by Pearson's χ^2 .⁶ Factors that were determined significant ($P < .05$) were then analyzed by stepwise logistic regression procedures to determine their independence.⁷ Independent variables were then used to construct a model for coccidioidal risk, P , through the following equation:

$$\ln(P/1 - P) = B_0 + B_1X_1 + B_2X_2 + \dots + B_nX_n$$

where \ln is the natural logarithm; B_1, B_2, \dots, B_n are regression coefficients estimated from the data in a stepwise procedure, and X_1, X_2, \dots, X_n are the individual factors being assessed. The degree to which any single factor correlates with other factors as predictors of disease is based on the coefficient value (B), with B_0 being the equation constant. Relative risk factors are based on a scale ranging from zero to one in which a value of one represents the highest risk of disease.

Results

During the 18-month period, our questionnaire was distributed to 556 patients. Of the 269 patients who received serologic evaluation and skin testing, coccidioidomycosis was diagnosed in 36 (13%). Of these, 26 were diagnosed serologically and in 10, skin tests converted from negative to positive within a month. The diagnosis was indeterminate for the remaining 287 patients.

A total of 40 questions and 6 routine laboratory results—including roentgenographic studies—produced responses for 11 that were significantly associated with cases of coccidioidal infection. These were erythrocyte sedimentation rate, male gender, "red lumps on shins," years of residence in an endemic region, acuteness of symptoms, number of peripheral blood lymphocytes, total peripheral blood leukocyte count, abnormal roentgenogram of the chest, chest pain with breathing, fever, and hoarse voice. When these factors were subjected to logistic regression procedures, six were identified as independent (Table 1). Erythrocyte sedimentation rate was found to have the greatest individual predictive power, with 53% of the infected population having a value of greater than 28 mm per minute. Men constituted 58% of cases even though they represented only 34% of the total population. The variable, "red lumps on shins," was only present in 20% of cases but its prevalence was even lower (5%) in noncases. The other three independent factors—length of residence within the endemic region, duration of symptoms, and total number of peripheral blood lymphocytes—were all inversely related to the likelihood of coccidioidal infection.

Several findings were common in both patients with coc-

cidioidal infection and other patients as well so that their specific association with coccidioidal infection was not statistically significant. These included decreased energy level, headache, and fatigue, which occurred in 88%, 86%, and 81% of patients with coccidioidomycosis and in 85%, 69%, and 85% of noncases.

Relative risk distributions for patients with and without coccidioidal infections are shown in Figure 1. It can be seen from these histograms that the risk of disease among the negative case group (mean risk value = .21) closely resembles that of the group for whom infection was indeterminate (mean risk value = .25). In contrast, the distribution for cases (mean risk value = .52) was shifted toward the positive predictive end of the scale. Of the 25 patients who exhibited four (having a relative risk of 0.6 or greater) of the six predictors, 15 (60%) were diagnosed with coccidioidomycosis.

Discussion

This prospective study indicates that some symptoms and other early findings in patients seeking medical attention for respiratory complaints are significantly associated with coccidioidal infections. Because this study was done in predominantly healthy college students within an area endemic for coccidioidomycosis, the general relevance of these findings to other regions of the country or to other patient groups will necessarily require substantiation. Similarly, the instrument

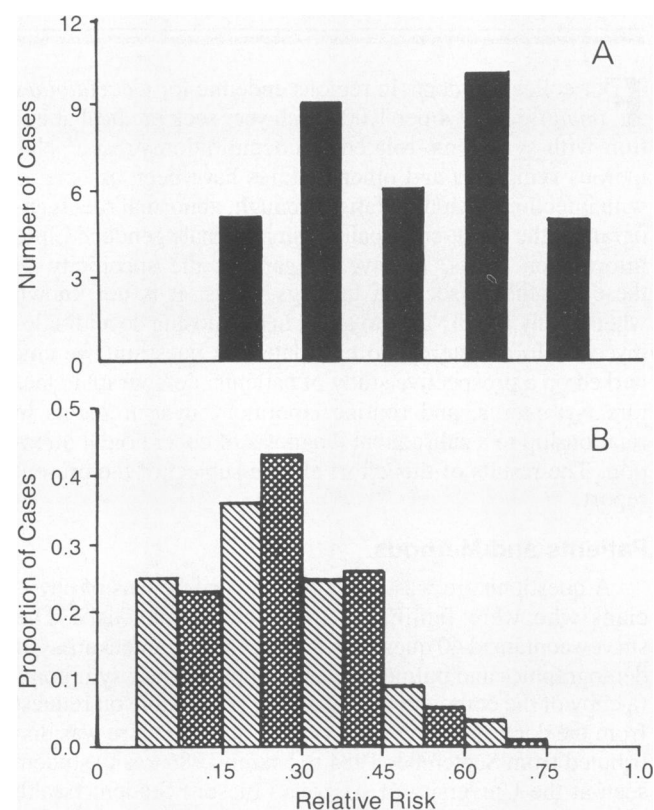


Figure 1.—The graphs show the distributions of the estimated likelihood of coccidioidal infection among 556 patients seeking medical attention for symptoms suggesting the possibility of coccidioidomycosis. The relative risk values are based on a standardized scale from 0 to 1 in which 1 represents the highest risk of disease. Panel A represents the relative risk distribution of 36 patients diagnosed with coccidioidomycosis. Panel B represents the relative risk distribution for those in whom the evaluation for coccidioidal infection was negative (hatched bars, $n = 269$) and for those in whom infection was indeterminate (crosshatched bars, $n = 287$).

that we devised was relatively arbitrary, and surveys seeking other information or using other methods may obtain results different from those reported here. Nevertheless, these findings indicate that at least under certain circumstances associations exist.

Some of these associations corroborate previous clinical impressions. As examples, fever, an abnormal roentgenogram of the chest, chest pain with breathing, having a skin rash (general), a recent arrival to an endemic region, an elevated erythrocyte sedimentation rate, and male gender were all found to be significantly more frequent in patients with coccidioidomycosis in our study. Other associations had not been previously noted, however. These included brevity of symptom duration before seeking medical attention, absence of a hoarse voice, and a decreased number of total peripheral blood lymphocytes. Several other complaints such as headache and fatigue, although found frequently in coccidioidal patients, were also frequent in patients in whom coccidioidal infection was not diagnosed and therefore did not discriminate among the groups. It is possible that our diagnostic methods may have missed some cases. Thus, with more sensitive methods, some additional symptoms might have been found to correlate with coccidioidal infection.

When subjected to logistic regression analysis, six variables emerged that appeared independent and could be used to estimate relative risk. Although the design of our study

resulted in a large number of patients in whom the possibility of coccidioidal infection could not be satisfactorily assessed, the distribution of their relative risk was similar to that of noncases. This suggests that our model might have been substantiated even if the data were more complete. Despite the differences between cases and noncases, the separation was not sufficient to recommend this model's use as an isolated diagnostic tool. If other independent variables could be identified, however, the model's practical value might be improved. The current study suggests that additional efforts in this regard are warranted.

REFERENCES

1. Kerrick SS, Lundergan LL, Galgiani JN: Coccidioidomycosis at a university health service. *Am Rev Respir Dis* 1985; 131:100-102
2. Lundergan LL, Kerrick SS, Galgiani JN: Coccidioidomycosis at a university outpatient clinic: A clinical description. In Einstein HE, Catanzaro A (Eds): *Coccidioidomycosis: Proceedings of the 4th International Conference*. Washington, DC, National Foundation for Infectious Diseases, 1985, pp 47-54
3. Smith CE, Saito MT, Beard RR, et al: Serologic tests in the diagnosis and prognosis of coccidioidomycosis. *Am J Hyg* 1950; 52:1-21
4. Wieden MA, Galgiani JN, Pappagianis D: Comparison of immunodiffusion techniques with standard complement fixation assay for quantitation of coccidioidal antibodies. *J Clin Microbiol* 1983; 18:529-534
5. Smith CE, Whiting EG, Naker EE, et al: The use of coccidioidin. *Am Rev Tuberc* 1948; 57:330-360
6. Szulc S: Sampling, chap 19, *Statistical Methods*. Oxford, Pergamon Press, 1965, pp 537-546
7. Cox DR: Regression models and life tables. *J R Stat Soc (B)* 1972; 34:187-220